IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

Wayne P. Franco

Serial No.: 09/828,330

Filed: April 6, 2001

For: **METHODS OF USE OF FIBROBLAST GROWTH FACTOR, VASCULAR ENDOTHELIAL GROWTH FACTOR AND RELATED PROTEINS IN THE TREATMENT OF ACUTE AND CHRONIC HEART DISEASE.**

Group Art Unit: 1647

Examiner: Christopher Nichols

#14

DECLARATION OF WAYNE P. FRANCO, M.D.
UNDER 37 C.F.R. §1.132

I, Wayne P. Franco, M.D., hereby declare that:

1. I am the named inventor on the above-referenced patent application.

2. I received a Bachelor of Science of Biology at Trinity College, Hartford, Connecticut in 1976, and an M.D. at Georgetown University, 1980.

3. I am currently practicing as a specialist in Internal Medicine (Board Certified), employed in Middletown, CT, and am on staff at Middlesex Hospital.

4. Prior to the instant invention, the delivery of angiogenesis factors involved invasive intracardiac delivery techniques or intravenous delivery. Intravenous delivery, though feasible, requires a longer pathway prior to being available to the coronary vasculature. Moreover, administration by injection is generally uncomfortable and cumbersome for the patient, and such techniques tend to be expensive.

5. As one skilled in the art would recognize, macromolecules such as proteins, peptides, and notably growth factors, frequently are too metabolically labile to be administered orally. Upon entering the stomach, the acidic environment and the presence of enzymes rapidly degrade the proteins and peptides.

6. Research has demonstrated that large-molecule agents are absorbed naturally by the lungs, and once absorbed in the lung, they pass readily into the bloodstream without the need for enhancers used by other noninvasive routes (See Patton, "Deep lung delivery of therapeutic proteins," *Chemtech*, Dec., 1997; Patton, *Adv. Drug Delivery Rev.*, **1996**, *19*, 3).

7. One familiar with cardiopulmonary physiology would recognize that upon inhalation, air passes through the trachea, which branches into successively smaller tubes (constituting the bronchial network), and eventually reaches tiny air sacs known as alveoli. The large surface area of alveoli allows oxygen to be distributed deep within

the lung tissue, from which oxygen passes into the bloodstream via an extensive capillary network.

8. A growing quantity of safety data indicates that the pulmonary route of delivery for therapeutic proteins is safe for patients with either healthy or diseased lungs. (*See* Patton, "Deep lung delivery of therapeutic proteins," *Chemtech*, Dec., 1997(citing Patton, *et al.*, *Respir. Drug Delivery*, **1994**, IV, 65; Kohler, *Aerosol Med.* **1994**; *7*, 307; and Adjei, A.L. *J. Aerosol Med.* **1995**, *8*, 131)).

9. To practitioners familiar with pulmonary drug delivery systems, it is apparent that dry powder inhalers, for example, provide many advantages over other routes of administration, particularly for overcoming recognized problems with systemic delivery of peptides, proteins and related compounds such as growth factors. Dry powder formulations of proteins and peptides, administered through a pulmonary delivery system, avoid metabolic degradation of the active drug species in the stomach and gut, or in the first-pass hepatic metabolism. Importantly, dry powder formulations tend to exhibit high drug volume delivery per dose, low susceptibility to microbial growth, and, in addition, tend to be applicable to both soluble and insoluble drug species. Also, many macromolecular drug species are more stable as solids than as liquids.

10. U.S. Patent No. 5,254,330 to Ganderton, *et al.* describes the carrier formulations for the dry powder inhalation of various pharmacological agents, particularly for agents not conveniently

administered by other routes. Examples of agents amenable for use with these carriers include sympathomimetic amines, sedatives, anti-inflammatory agents, and especially peptides and growth hormones, such as insulin and ACTH and LHRH analogues.

11. Though the Ganderton patent teaches a crystalline sugar carrier other common carriers include inorganic salts (*i.e.*, sodium chloride or calcium carbonate), organic salts (*i.e.*, sodium tartrate or calcium lactate), organic compounds (urea or propylidene), monosaccharides (lactose, mannitol, arabinose, or dextrose), disaccharides, or polysaccharides. See U.S. Patent No. 4,409,237.

12. Moreover, biological macromolecules, including proteins and peptides, can be combined with other additives or carriers that serve a variety of functions. For instance, the additives or carriers can be combined with the active agent powder to dilute the powder to an amount suitable for delivery; to facilitate the *in vivo* release of the active agent; to improve the properties of the preparation; for stability; to adjust the pH; or to improve the taste of the drug. See U.S. Patent No. 6,436,902 to Backstom. Examples of potential additives include mono-, di-, and polysaccharides, sugar alcohols and other polyols, such as lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol, and starch.

13. The mechanism of activity of growth factor proteins such as FGF and VEGF is well characterized. For example, there are two specific

receptor for VEGF: Flk-1/KDR and Flt-1. VEGF bound to receptors on endothelial cells is known to act as a direct inducer of angiogenesis both *in vivo* and *in vitro*.

14. Hypoxia (lack of oxygen) is a known factor that stimulates both secretion of protein growth factors and receptors for growth factors such as, for example, VEGF. For VEGF, the response of VEGF receptors to hypoxia varies from selective stimulation of Flt-1 to inhibition of Flk-1/KDR. *In vivo* studies in rats have demonstrated that in an oxygen-free environment, there is a quantitative increase in VEGF and Flt-1 receptors in hepatocytes. (*See* Josko, *et al.*, "Vascular endothelial growth factor (VEGF) and its effect on angiogenesis," *Med Sci Monit.*, **2000**; 6(5); 1047-1052).

15. Given that hypoxia enhances VEGF activity as decribed in ¶ 14 above, VEGF activity is largely dependent on the presence of the appropriate receptors. Appropriate receptors for VEGF are stimulated in oxygen-free environments. In contrast to the hypoxic environment normally encountered in damaged heart tissue (the usual site of administration of protein growth factors such as FGF and VEGF during highly invasive open heart surgery) the nasal cavity, throat and lungs are highly oxygen effused and therefore do not constitute an environment that would lead to significant VEGF of FGF activity.

16. To ensure that there are no side effects in the mouth of patients treated with the growth factor proteins according to the invention

disclosed and claimed in my patent aplication, the patient can immediately rinse the mouth area with water after inhalation. Once inhaled into the lungs, the angiogenic factors would be delivered to the left atrium, left ventricle, and then be available for an effect on the coronary vasculature.

17. In contrast to a pulmonary route of delivery, an intravenous route is disadvantageous for two primary reasons: (1) it is invasive, and (2) it requires a much longer pathway prior to being available to the coronary vasulature. Use of pulmonary delivery of therapeutic doses of protein growth factors is significantly less invasive than administration during surgical procedures and, as a consequence, can be administered more often, even routinely, providing significant therapeutic benefit to patients.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 1/21/03

Wayne P. Franco

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